OUTCOME OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN GOVERMENT RAJAJI HOSPITAL

DISSERTATION SUBMITTED FOR

MD BRANCH VII [PAEDIATRICS]
PART II

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI

MARCH 2009

CERTIFICATE

This is to certify that the dissertation entitled "**OUTCOME OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN GOVERTMENT RAJAJI HOSPITAL**" is a bonafide record of work done by **Dr.P.GUNA** in the Institute of Child Health and Research Centre, Govt. Rajaji Hospital, Madurai Medical College, Madurai, and is submitted to the Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch VII) in Paediatrics .

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DECLARATION

I, Dr.P.Guna solemnly declare that the dissertation titled **OUTCOME OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN GOVERTMENT RAJAJI HOSPITAL** has been prepared by me. This is submitted to the Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch VII) in Paediatrics .

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CONTENTS

INTRODUCTION

Acute Lymphoblastic Leukemia [ALL] is the most common childhood malignancy. It accounts for one fourth of all childhood cancers and approximately 75% of all cases of childhood leukemia [1]. Before the advent of effective chemotherapy in 1960s ALL is usually a fatal disease .With modern intensive protocols at least in the developed countries 70%-80% of children with ALL are now being the long term survivors. However this is not the case in developing countries where 80% of children with ALL reside. Approximately 8000 cases of childhood ALL diagnosed in each year in India.[3] Only 25% receive appropriate treatment. Studies from India have shown that 40%to 60% of patients treated in a paediatric oncology centre on an affordable protocol with manageable toxicities can be cured.[27,37,45]

There are several reasons for these poor results including poverty, lack of awareness, lack of access to adequate medical care, lack of adequately trained personnel and competent oncology units. These factors lead to delayed and sometimes improper diagnosis, delayed referrals, poor compliance, inadequate or inappropriate therapy and poor outcome

EPIDEMIOLOGY: The incidence of childhood ALL is approximately 3-4 cases per 100,000 children under the age of 15 years [20] .It is most common between ages of 1 and 5 years with a peak at 3-4 years [1,3]. The incidence of ALL is higher in boys than in girls

ETIOLOGY: The etiology of ALL is not known in virtually all cases [2].Environmental factors such as electro magnetic radiation, ionizing radiation, pesticides and infectious agents such as Epstein Barr virus have been implicated. Genetic disorders predisposing to leukemia include trisomy 21, congenital immunodeficiency, ataxia-telangiectasia, bloom syndrome and fanconi's anemia. Siblings of children with ALL have a 2-4 fold increased risk of developing ALL than do children in the general population. The risk is being high among homozygotic twins especially during the first few years of life.

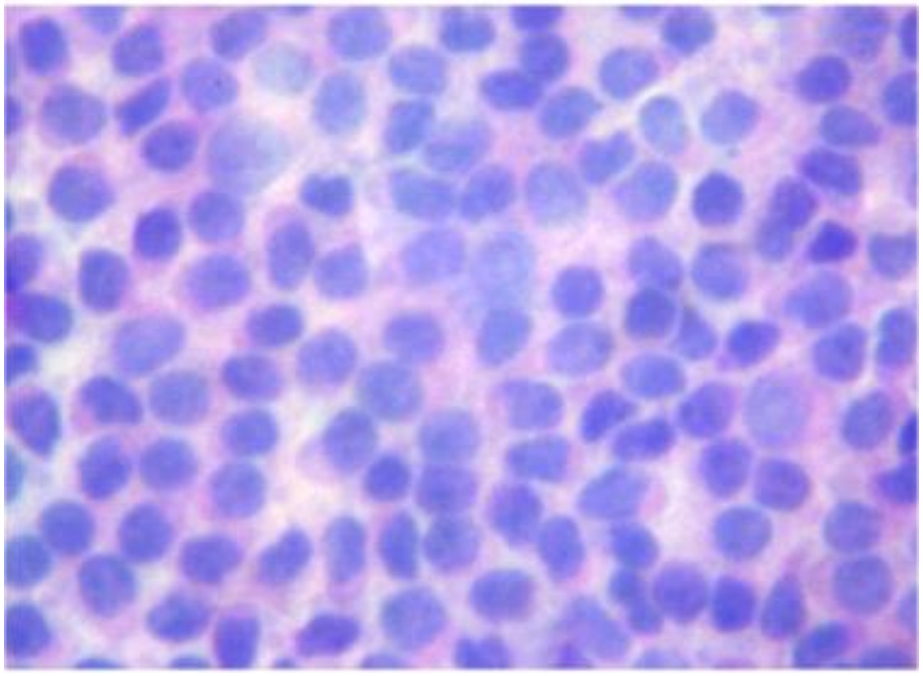


FIGURE 1 - CYTOLOGY FROM TESTICULAR TUMOUR SHOWING ATYPICAL LYMPHOBLASTIC INFILTRATION (PAP STAIN - H 609/06)

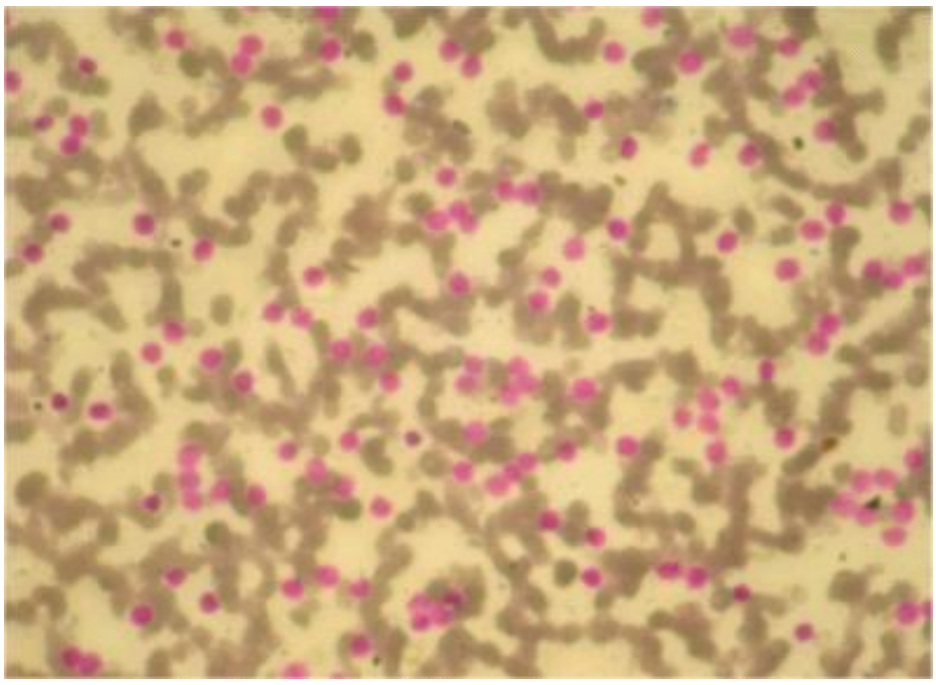


FIGURE 2 - HYPERLEUKOCYTOSIS IN PERIPHERAL SMEAR IN ALL. LEISHMAN STAIN X 100 H 926/05

CLASSIFICATION: 1.Morphological:

Cytological features	L1	L2	L3
Cell size	Small cells predominate	Large, heterogeneous in size	Large and homogeneous
Amount of Cytoplasm	Scanty	Variable, often mod. Abundant	Moderately abundant
Nucleoli	Not visible, or small and inconspicuous	One or more present, often large	One or more present often prominent
Nuclear Chromatin	Homogeneous in any one case	Variable, heterogeneous in any one case	Finely stippled and homogeneous
Nuclear Shape	Regular, occasional clefting or indentation	Irregular, clefting and indentation	Regular oval to round
of cytoplasm	Variable	Variable	Intensely basophilic
Cytoplasmic vacuolation	Variable	Variable	Prominent

Cytochemistry:

Sharma JS and Mohindroo S had found that the concordance with morphology alone was 75% which improved to 92% when cyto chemistry is included

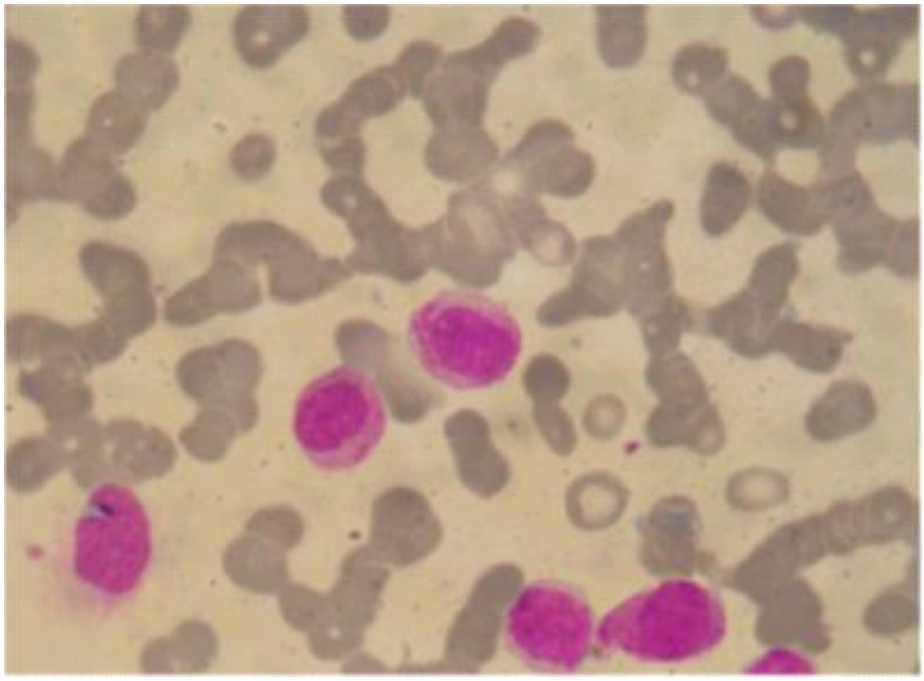


FIGURE 3 - MYELOBLASTS WITH MULTIPLE AUER RODS IN AML M3 LEISHMAN STAIN X 1000 H 1069/05.

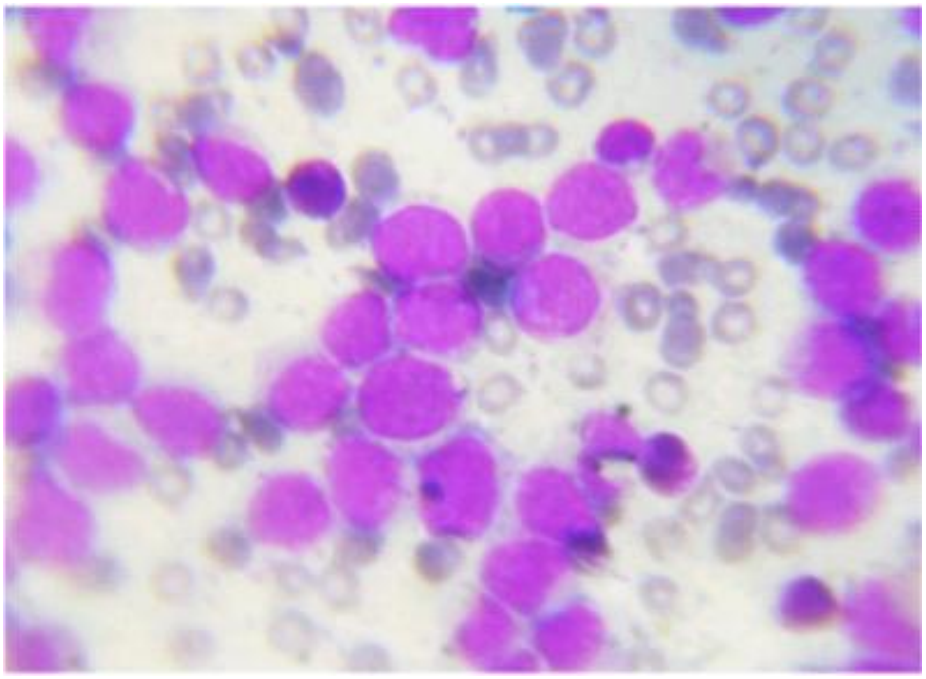


FIGURE 4 - ALL L2 BLAST CELLS VARIES IN SIZE AND AMOUNT OF CYTOPLASM. LEISHMAN STAIN X 450 H 1258/06.

The stains commonly used are

1. Myeloperoxidase (MPO) 2.Sudan Black B (SB] 3.Non specific esterase (NSE] 4.Specific esterase 5. PAS

Lymphoblasts are acid Schiff positive in block pattern. The myeloblasts are PAS negative but myeloperoxidase and Sudan block positive. The monocytes are nonspecific esterase positive. The terminal deoxy transferase is positive in 95% of the cases of lymphoblasts and only in 5% of the myeloblasts

Snower DP et al, [65] in their study of 51 cases found that the sensitivity and specificity of the PAS stain alone for lymphoblastic leukemia was 52% (15 true positives of 29) and 81% (four false positives), respectively. The sensitivity of a cytochemical-staining combination of PAS positivity and myeloperoxidase, Sudan black B, and alpha-naphthyl butyrate esterase negativity in defining cases of lymphoblastic leukemia remained at 52%; however, the specificity of this combination for lymphoblastic leukemia was 100% (no false positives). Thus, a positive PAS stain, in combination with negative myeloperoxidase, Sudan black B, and alpha-naphthyl butyrate esterase stains, continues to have a diagnostic role in the

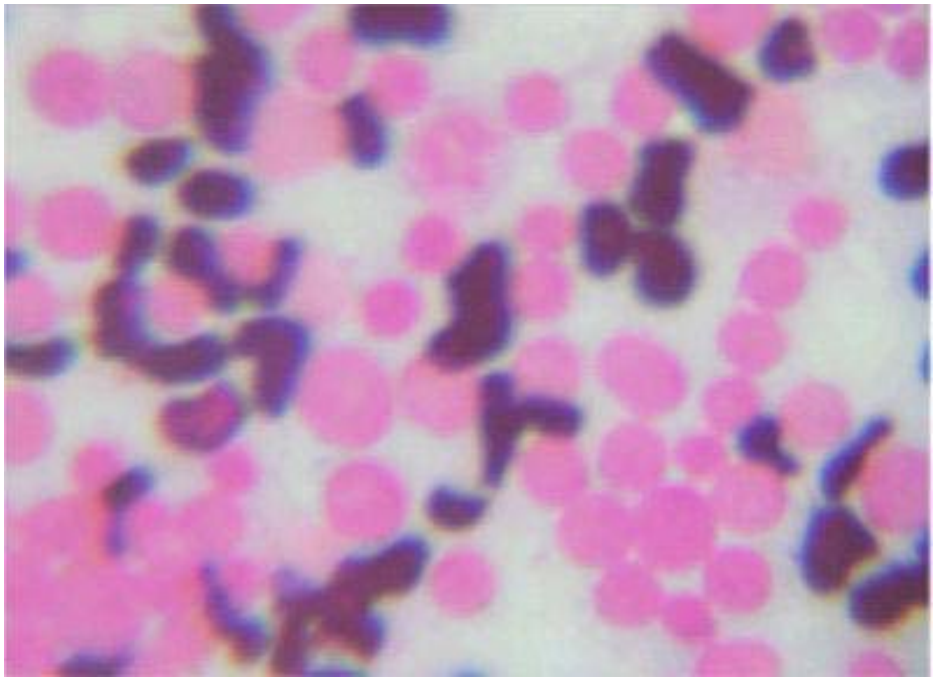


FIGURE 5 - MYELO PEROXIDASE STAIN SHOWING NEGATIVE STAINING IN CYTOPLASM IN ALL X 450 H 350/05.

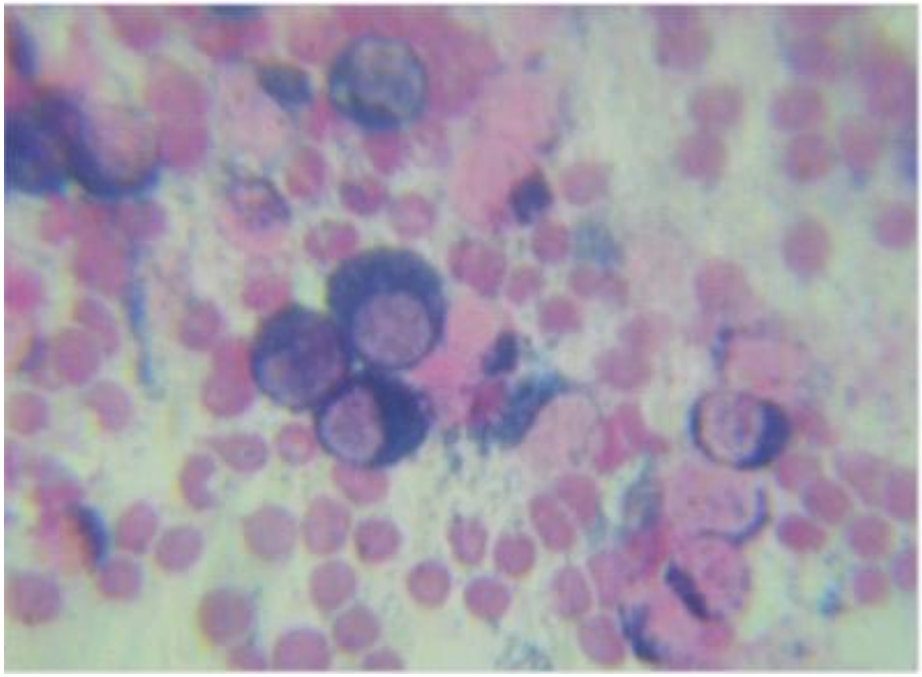


FIGURE 6 – SUDAN BLOCK B STAIN SHOWING INTENSE BLACK GRANULAR STAINING IN CYTOPLASM IN AML M3 X 450 H 1069/05

distinction between lymphoblastic and myeloblastic leukemia, and greater immunologic sophistication serves to support this position.

IMMUNOLOGIC SUB TYPING:

It is usually based on reactivity with a panel of lineage –associated antibodies [1,8].About 85% of ALL are derived from progenitor cells.15% from T cells,1% from B cells [5]

Small percentage with both lymphoid and myeloid markers [1,8]

Subtype	Antigen expression
Early pre -B	CCD22,CD79a,CD19+CD22Cig-[mu] sIg-
Pre B cell	cIg + [mu]
B cell	SIg+, SIg [kappa], SIg [lamda]
T cell	CCD23+,CD7+,CD5+, CD2+,CD3+

[CCD22-cytoplasmic CD22, CIg—cytoplasmic immunoglobin

SIg- surface immunoglobin, mu- mu heavy chain protein, Kappa- kappa light chain protein, lambda-lambda light chain protein]

CYTOGENETIC ABORMALITIES

Genetics of leukemia:

Genetic alterations are at the base of all leukemias. Specific chromosomal changes can be identified now in more than 90% of the ALL cases [1]. Most of them are reciprocal translocations. These abnormalities correlate with the blast cell biologic properties, clinical features and have a correlation with the prognosis of the disease. Methods to diagnose genetic alterations are as follows

1. cytogenetics 2. fluorecent in situ hybridization 3.flow cytometry-measures total cell content, which correlates with chromosomal number.4 Reverse Transcriptase Polymerase Chain Reaction [RT-PCR]. It is a very sensitive and specific test to detect minimal residual disease and relapse

Importance of cytogenetic and molecular cytogenetic studies evaluation [34,35] :

1. Diagnosis and risk classification- allows better correlation of tumor characteristics with clinical behavior
2. Specific therapy-e.g. ATRA for t [15,17] inM3 has provided the first example of therapy directed at the underlying molecular defect

3. Monitoring minimal residual disease: the exquisite sensitivity of RT-PCR assays has provided the ability to detect residual leukemia at previously unattainable levels.
4. Diagnosis of relapse: RT-PCR helps too detect relapses in patients with known molecular lesions before morphological relapses

Hyperdiploidy, Trisomies of 4, 10 chromosomes and translocation t [12,21] favor good prognosis. Hypodiploidy, translocations t [9,22], t[4,11] favor poor prognosis [21]

CLINICAL MANIGESTATIONS:

The most common symptoms and signs are usually the manifestations of the underlying anemia [pallor, fatigue], thrombocytopenia [petechiae, purpura and bleeding] and neutropenia [fever and infections] Extramedullary disease commonly present as lymphadenopathy and hepato-splenomegaly in >60% of case [20].

Adverse factors include: male sex, age less than 1 year and more than 9 years, count more than 50,000 cells per cu mm, L3 morphology, CNS disease, mediastinal mass, hypoploidy, Philadelphia chromosome and t (4;11), persistence of blast on day 7 or 14 after start of therapy. Advanced age and high WBC count at the time of diagnosis have a significantly

adverse prognosis. Unfavorable cytogenetic abnormalities in ALL include t (9;22), t (4 ;11) and q21, a count >1000/cumm on peripheral blood after 7 days of prednisolone and one dose of intrathecal methotrexate and minimal residual disease>1%[13,64]

TREATMENT: The average duration of treatment is two to two and a half years. The protocol used for treatment of ALL in India is MCP-841

INDUCTIONS-1 (month 1 and month 3)

L asparginase	6000 units/M^2	alternate days
Vincristine	1.4mg/M^2	Once a week-5 doses
Daunomycin	30mg/M^2	days 8,15,28
Prednisolone	40mg/M^2	days 1 to 28
I.T. Methotrexate	12mg/M^2	days 1,8,15,22,28

INDUCTION-2 (month 2)

Cyclophosphamide	750mg/m^2	days 1,15
6-Mercaptopurine	75mg/m^2	days 1 to 7, 15 to 22
I.T Methotrexate	12mg/m^2	days 1,8,15,22
Cranial radiotherapy	1200cGy	days 5 to 15

CONSOLIDATION (month 4)

Vincristine	1.4mg/m^2	days 1, 15

Cyclophosphamide	750mg/m^2	days 1
Daunomycin	30mg/m^2	days 15
Cytarabine	100mg/m^2	days 1,2,3 & 15,16,17
6-Mercaptopurine	75mg/m^2	days 1 to 8 & 15 to 22

MAINTENANCE: **(one in three months x 6 cycles)**

L asparginase	6000 units/M^2	days 1,3,5,7
Vincristine	1.4mg/M^2	days 1
Daunomycin	30mg/M^2	days 1
Prednisolone	40mg/M^2	days 1 to 7
6-Mercaptopurine	75mg/M^2	days 15-90 (5 days/week)
Methotrexate	15mg/m^2	days 15,22,29,….90 once a week

RELAPSE:

25% of children with ALL relapsed during or after completing chemotherapy. The main sites of relapse are bone marrow, CNS, and the testes. Features of relapse are a morphological shift from small L1 blasts to larger pleomorphic L2 to L3 blasts, additional changes in cytogenetics occurs in 10% of cases [43]

Treatment after relapse: Must be more aggressive to overcome the problems of drug resistance. After entering into second remission bone marrow transplantation offers chances of cure

OUTCOME:

The five year survival rates of the patients with ALL in reputed cancer institutes of India Vary from 45-55% [37,45].but the survival rate of cases in developed countries is about 80-85% [25]

REVIEW LITERATURE

REPORTING IN INDIA:

Population based data on the incidence of leukemia and other cancers in the developing countries are neither consistently available nor very reliable due to under registration and absence of organized registry .therefore hospital statistics in the developing countries provide the only available window to observe the disease pattern in the community [14,17]

EPIDEMIOLOGY:

Acute lymphoblastic leukemia is the common type of all leukemias of about 62.5%o 75% [1,9,18] **Age:** the most common age group of ALL at presentation was 2-6 Years [18] with a peak Around 3-4 years.[3,20] This peak is mainly due to the predominance of pre B ALL cases in this age group.

Sex: Incidence of ALL is higher in boys than in girls. Male: female ratio 1.3:1[1,3,18]

Etiology: various studies have not been able to conclusively prove any definite etiological risk factor for leukemia [19,20]. Down syndrome is the most common syndrome associated with 15 fold increase in risk of leukemia in first decade [3]

CLINICAL FEATURES:

Fever is seen in 100% of case of leukemia at the time of Presentation [1] In Indian studies about 56% of ALL present with fever as the main complaint [16,18]. Bleeding is seen in 30-40% of the leukemias at the time of presentation [1,9]. Pallor is seen in 100% of cases in both Indian and western studies. Testicular involvement at the time of diagnosis is 25%of cases and in 15% of cases who completed the treatment [42,44,47].But it can vary from 1-40% [64]

Hepatosplenomegaly was seen in 68% of cases [10] in western literature. But in Indian literature it is about 87% [45].western studies state that **lymphadenopathy** is present in 50% [9,10] of cases. But Indian studies quote from 76%-85% [15,18,45]. **Bone and joint pain** were in 28%. In Manipur study it is about 46.7%.**Bilateral parotid swelling** with massive hepatosplenomegaly is associated with poor prognosis [49]

CNS COMPLICATIONS DURING LEUKEMIA:

This occur either due to the disease per se or of the side effects of therapy. CNS Involvement is reported to occur more in AML than ALL-the figures being 5%[10] for ALL and 5-15% for AML[29].seizures have been reported in 8-13% of the patients [29]. The most common cranial nerves

involved due to leukemic infiltration are 2, 6, 7. Ophthalmic complications are seen in 9% of the children. Thrombosis and hemorrhage occurs in 1-2% of children. The majority of such complications occur in the third and fourth weeks of induction [29].According to Singh et al the 7^{th} cranial nerve was the most common involved. The Revised criteria for CNS involvement at diagnosis, as quoted by Mastrangelo R [66] is as follows -

CNS-1 - one blast cell

CNS-2 - <5 WBC/micro litre with blasts cells

CNS-3 -> 5 WBC/micro litre with blasts or Cranial nerve involvement

INFANTILE LEUKEMIA:

Leukemia in infancy constitutes 3-5% of children with leukemia. Infantile leukemia has special biologic characteristics [9]. Western literature quotes that AML of the M4 or M5 type is more common in infantile leukemia with a relative female preponderance [9,10].congenital leukemia was diagnosed only in 2 of the 115 cases reported by Reaman et al most of them were of AML type [30].However in a study conducted by somjee et al the department of medical oncology Tata Memorial hospital Mumbai, on cases of infantile leukemia, it was found that ALL-L1 was more common. With a relative male preponderance was reported [31] these patients had significant organomegaly, hyperleucocytosis and hepato-splenomagaly.

LAB PARAMETERS:

Despite the advent of modern ancillary techniques, morphologic examination and cytochemical staining of well-prepared air-dried peripheral blood smears and bone marrow smears are critical in the pathologic diagnosis and classification of acute leukemias. Hemoglobin is less than 10mg/dl, the percentage varying from 80-96% in all the studies for ALL [1,18]. The total count is more than 50000 at the time of presentation in 17-25% of the cases of ALL [10,11,18]. The total count more than >50,000 is a poor prognostic factor for ALL .In Manipur study[18] this was between 36-46%.15 % of patients present with marked hyper leukocytosis. One third of patients present with platelet count less than 25000 x 10^6/litre[33] and less than 50,000 in 50% of cases Peripheral blasts may not be observed in 25-30% of the cases [26]. But in a Indian study [18] it is about 18.7%.

MORPHOLOGIC CLASSIFICATION:

According to Singh et al [18] L1 constituted 63.3% of the cases and L2 36.7%. Other reviews quote L1 being about 80-85% L2 about 15% and L3 1-2% [1,9;16] L1& L2 morphological types bear no relationship to immunological type or other prognostic factors.

Loffler H et al had noted that the identification of the L3 variant is of major importance. According to studies there is a high but not universal

correlation of the L3 phenotype as defined by morphology with the immunologically defined B-ALL with surface expression of immunoglobulins [67].

The prognostic significance of being able to distinguish between L1 & L2 morphologic subtypes has never been fully proven. Findings with established prognostic significance, such as favourable and unfavourable cytogenetic alterations occur in both L1 & L2 .Similarly immuno phenotypes tht may be of prognostic significance do not correlate well with L1 & L2 morphology.

IMMUNOPHENOTYPING

The development of monoclonal antibody against cell surface markers of blood cells and their conjugation with certain flurochromes markedly contributed to the application of flow cytometry in the study of normal haematopoiesis.

Commitment to B cell differentiation is indicated by the appearance of CD19 & CD10.Typical phenotype of peripheral B lymphocyte is CD19+, CD20+, CD21+ and CD22+.Majority of blood T lymphocytes are CD2+, CD3+ and CD7+ and express either CD4 or CD8.

CD33 is the earliest marker for myeloid differentiation. Immature myeloid cells become CD13+ followed by appearance of CD15 and CD11b.

in contrast monocytes are strongly CD33+ and weakly CD15 and CD4 positive.

Expressions of myeloid antigen marker are slightly more frequent in B-lineage ALL than in T-lineage ALL but have no prognostic value.

T cell ALL are subclassified into different stages corresponding to normal thymocyte development , the early subtype is negative for surface CD3 and is either double positive or double negative for CD4 and CD8 , the later subtype is surface CD3+and positive for CD4 or CD8 and not both. Recent studies do not find any prognostic differences in this sub classification of T cell ALL.

Lymphoblast lymphomas and ALL have more similarities than differences in pathology, immunophenotype, and genotypes and hence they have been regarded as process falling within the spectrum of a single disease entity. ALL and lymphoblast lymphomas are grouped under the category labeled lymphoblastic leukemia / lymphoma in the Revised European and American Classification of Lymphoid Neoplasm's (REAL) and in the WHO Classification Scheme

The WHO classification does not group the ALL together, but separates them under three broader categories of lymphoid disease:

1. Precursor B cell

2. Precursor T cell

3. Mature B cell neoplasms

Bucheri V etal had proposed a scoring system for a diagnosis of biphenotypic leukemia [68]

Points	B cell	T cell	Myeloid
2	CD79a ,CD 22 cytoplasmic IgM	CD3	MPO
1	CD 19 ,CD10	CD2 CD5	CD33 CD13
0.5	TdT	TdT ,CD7	CD14 ,CD15, CD11c,CD11b

Biphenotypic acute leukemia is established when score from two separate lineages score than 2. Recent studies include CD117 as a highly specific myeloid marker equivalent to 2 points and T cell receptor a highly specific T cell marker with 2 points

CYTOGENETIC ABNORMALITIES:

It is now possible to demonstrate abnormalities in chromosome number or structure in over 90% of the cases of ALL[1] however even in the best of

labs successful karyotyping are obtained only in 30-50% of the cases analyzed[33,34,35]

Several mechanisms contribute to tumor formation [34]

1. Whole chromosome duplications-most frequent abnormality. This is seen in approximately 40% of cases. the most common whole chromosome duplications included X, 4,6,10,21

2. Whole or partial chromosome deletion:

3. Translocations : result in the creation of either a tumor specific chimeric protein as a result of gene fusion leading to transcriptional dysregulation of the involved gene

In a study conducted by Petkovic et al [36] on 55 children with ALL, they detected abnormalities in 63.6% of the cases. All children less than six months, 57.8% in the age group 1-10 years and 85.7% in the age group more than 10 years had aberrations. Common abnormalities detected were : hyperdiploidy more than 50, del 6and t[1,19]. In an analysis of 94 bone marrow karyotypes analysis of children with acute leukemia by Heimetal 68% of All had chromosome abnormalities [38]. In ALL the most common abnormality was hyperdiploidy[49%] followed by deletion if 6q in 10.2% of

the cases and re-arrangements of 12p in 6.4% only 0.7of hyperdiploidy where as 23.4%of cytogenetically and 30% of those with other structural abnormalities relapsed

PROGNOSTIC FACTORS & RISK ASSESSMENT:

ALL:

Favourable risk factors include female sex, age 1 to 9 years, WBC count less than 50,000 cells per cumm, LI morphology, and hyperdiploidy.

Adverse factors include: male sex, age less than 1 year and more than 9 years, count more than 50,000 cells per cumm, L3 morphology, CNS disease, mediastinal mass, hypoploidy, Philadelphia chromosome and t (4;11), blast on day 7 or 14 after start of therapy. Advanced age and high WBC count at the time of diagnosis have a significantly adverse prognosis. Unfavorable cytogenetic abnormalities in ALL include t (9;22), t (4 ;11) and q21. A count >1000/cumm on peripheral blood after 7 days of prednisolone and one dose of intrathecal methotrexate and minimal residual disease>1%

RISK ASSESSMENT

IAP NATIONAL GUIDE LINES: [3]

High risk:

1. Age less than 1year and more than 10
2. CNS or testicular disease at presentation
3. WBC count at presentation > 50000/cumm
4. T-lineage ALL, pre-preALL
5. philadelphia positive ALL

Non high risk:

1. Age between 1 to 10 years
2. No CNS or testicular disease at presentation
3. WBC count <50000/cumm
4. CALLA positive ALL

NATIONAL CANCER INSTITUTE'S RISK CLASSIFICATION:

[B precursor ALL][62]

Standard

1. WBC count <50000/ul 2.age 1.00-9.99years

High risk:

1. WBC count >50000 2.age <10 years

POG RISK CLASSIFICATION: [55]

Low risk:

NCI consensus age and WBC criteria

Absence of adverse translocations,

Absence of CNS disease and testicular disease,

The presence of either the TEL-AML1 translocation or trisomy of chromosomes 4 and 10.

High-risk group:

Absence of favorable translocations

Presence of CNS or testicular leukemia,

The presence of MLL gene rearrangement,

Unfavorable age and WBC count

Very high-risk:

Presence of the t(9;22)

M3 marrow on day 29 or M2 or M3 marrow on day 43,

Hypodiploidy (DNA index <0.95).[122]

BFM:

STANDARD RISK:

Prednisone good responders (those with absolute blast count <1000/μL at the end of the prophase)

HIGH RISK:

Patients with an absolute blast count of 1000/μL or greater at the end of a 7-day

1. Prednisone prophase (prednisone poor responders)
2. All patients with the t (9;22) ,t[4,11]
3. MRD>10-3

MODERATE RISK

1. All patients with T-cell phenotype, mediastinal mass, or CNS involvement were considered
2. MRD <10>-3

PROGNOSTIC GROUPS UNDER CLINICAL EVALUATION

CLASSIFICATION SYSTEM FOR THE COG. [55]

Based on this analysis, patients with precursor B-cell ALL are initially assigned to a standard-risk or high-risk group based on age and initial WBC count (aged 1–9.99 years, and <50,000 WBC/μL is considered standard

risk). All children with T-cell phenotype are considered high risk regardless of age and initial WBC count. Early treatment response (assessed by day 7 or day 14 marrow morphology and end-induction MRD assessment) and cytogenetics are subsequently used to modify initial risk-group classification. NCI standard-risk patients with rapid morphologic response (day 14 M1 marrow) and MRD less than 0.1% and an M1 marrow on day 29 are assigned to one of two groups based on cytogenetics. Patients with either t(12;21) or trisomies of chromosomes 4, 10, and 17 are considered "standard risk-low while patients with neither of these two cytogenetics abnormalities are considered standard risk-average." Standard-risk patients with either slow morphologic response(either day 7 or day 14 M1 marrow) and/or MRD more than 0.1% on day 29 are assigned to a third group (standard risk-high) and receive a more intensive post induction treatment. High-risk patients with precursor B-cell ALL are divided into rapid-responder (rapid morphologic response and low MRD) or slow-responder groups. Patients are classified as very high risk if they have any of the following features (regardless of initial risk group): t(9;22), hypodiploidy less than 44 chromosomes, MLL translocation with a slow early morphologic response, M3 marrow on day 29 or M2 marrow and/or MRD greater than 1% at days 29 and 43.

THE DANA-FARBER CANCER INSTITUTE (DFCI) ALL CONSORTIUM is also testing a new risk classification system for patients with precursor B-cell ALL. All patients are initially classified as either standard risk or high risk based upon age, presenting leukocyte count and the presence or absence of CNS disease. At the completion of a five-drug remission induction regimen (4 weeks from diagnosis), the level of MRD is determined. Patients with high MRD (≥0.1%) are classified as very high risk and receive a more intensive post remission consolidation. Patients with low MRD (<0.1%) continue to receive treatment based on their initial risk-group classification. The goal of this new classification schema is to determine whether intensification of therapy will improve the outcome of patients with high MRD at the end of remission induction. Patients with T-cell ALL are treated as high risk, regardless of MRD status. All patients with MLL translocations or hypodiploidy (<45 chromosomes) are classified as very high risk regardless of MRD status or phenotype. Patients with the Philadelphia chromosome are treated as high risk, but receive an allogeneic stem cell transplant in first remission.

At ST. JUDE CHILDREN'S RESEARCH HOSPITAL, risk classification is based mainly on MRD level (assessed by flow cytometry)

after 6 weeks of remission induction therapy as follows: low risk (<0.01%), standard risk (0.01% to <1%),and high risk (≥1%).

T-cell Acute Lymphoblastic Leukemia

Historically, patients with T-cell acute lymphoblastic leukemia (ALL) have had a worse prognosis than children with precursor B-cell ALL. With current treatment regimens, outcomes for children with T-cell ALL are now approaching those achieved for children with precursor B-cell ALL. For example, the 5-year event-free survival (EFS) for children with T-cell ALL treated on the Dana Farber Cancer Institute (DFCI) Consortium ALL protocols was 75% compared with 84% for children with precursor B cell ALL Protocols of the former Pediatric Oncology Group (POG) treated children with T-Cell ALL distinctly from children with B-lineage ALL. The POG-9404 protocol for patients with T-cell ALL was designed to evaluate the role of high-dose methotrexate and the role of the cardio protectant dexrazoxane. The multi agent chemotherapy backbone for this protocol was based on the DFCI 87-001 regimen. Results of an interim analysis of the POG protocol led investigators to conclude that the addition of high-dose methotrexate to the DFCI-based chemotherapy regimen results in significantly improved EFS, due in large measure to a decrease in the rate of central nervous system (CNS) relapse. This POG study was the first clinical

trial to provide convincing evidence that high-dose methotrexate can improve outcome for children with T-cell ALL. High-dose asparaginase and doxorubicin were also important components of this regimen.

Infants with Acute Lymphoblastic Leukemia

Infant ALL is uncommon, representing approximately 2% to 4% of cases of childhood ALL [31]. Because of their distinctive biological characteristics and their high risk for leukemia recurrence, infants with ALL are treated on protocols specifically designed for this patient population. Despite intensification of therapy, long-term EFS rates from recent trials remain below 50%, and for those infants with MLL gene rearrangement the EFS rates continue to be in the 30% to 40% range. Common therapeutic themes of the intensive chemotherapy regimens used to treat infants with ALL are the inclusion of post induction intensification courses with high doses of cytarabine and methotrexate.

RELAPSE:

25% of children with ALL relapse after treatment.[1,16]. The main sites of treatment are bone marrow, CNS, and the testes. Features of relapse are a morphological shift from small L1 blasts to larger pleomorphic L2 to L3 blasts, additional changes in cytogenetics occurs in 10% of cases [43]

primary relapse has also been reported in anterior segment of the eye. according to VP Choudry et al the incidence of relapse is very high in the Indian scenario being about 30%[41].The reasons are 60% of the Indian children are high risk at the time of diagnosis, higher prevalence of T cell leukemia, less intensive chemotherapy and poor compliance. Relapses are classified as early if it occurs within the first 18 months, intermediate if it occurs between 18-36 months and late if it occurs after 36 months [24]. Most relapses in all occur in the first 5 years of diagnosis. Combined relapses [bone marrow and extra medullary] often occur later than isolated bone marrow. While isolated CNS relapse tends to occur within 3 years of diagnosis, testicular relapse after the treatment has been stopped. The survival of children with bone marrow and CNS relapse reported to be less than 20%.[43]

Testicular relapse:

According to Arya et al it is seen in 3% of cases in the UKALL study 12% of children developed testicular relapse over 15 years from 1972to 1987[47].children with early testicular relapse or during therapy had a worse prognosis. Incidence of biopsy proven occult testicular leukemia is estimated to be around 25% and that of overt disease is about 16% during the course of the therapy [44].The percentage increases after the full course of therapy is

completed. The lymphoblasts in the interstitium of the testis somehow [40] escape the onslaught of the drugs due to the presence of blood testis barrier.

Event free survival in the second remission is poor .Favorable factors include Isolated testicular relapse, combined bone marrow and extra medullary relapse, duration of Clinical remission more than 24 months, initial age at diagnosis between 2-6 years and WBC count below 10000 at the time of relapse [43,44].older age group, T cell disease and bone marrow relapse are poor prognostic factors. Studies conducted at Sweden reveals that the most important prognostic factor was the duration of the first complete remission [43,44].

SURVIVAL AND OUTCOME:

Since the introduction of total therapy as first described by Pinkel [23] in 1971 the prognosis in ALL has improved from less than 5% survival before 1965 to 25%-50% during the 70s to 70% during the 80s and 80% for children in the 1990s.[1]

It is estimated that only one out of ten children with acute leukemia receive any kind of treatment in these less privileged countries. Hence even though 70% of childhood ALL is currently curable, it is not 70% Curable World wide, since 90% of the world children do not have access to curative treatment [15].

According to LS Arya et al the survival rate at All India institute of medical sciences is 51% [16]. Five years survival for ALL patients in USA is 87.8% and 10 year survival is 83.8% [25]. A study from vellore [27] at 2003 five year overall gives survival rate is 59.8%, event free survival rate is 56% and disease free survival is 53.9%. In another study from china conducted at 2006 the 5 years EFS is about 51.50%[12].In the study from Chennai [59] the EFS calculated for 4 years is 18%, 3 years 31% 2 years is 41%. Many other Indian literature reviews reveals the same

Reasons attributed to decreased survival in India compared to the developed countries are

1. The financial burden of treatment
2. Poor compliance and large no of drop outs
3. Lack of availability of good supportive care and poor tolerance to chemotherapy by the malnourished patients
4. High incidence of infections
5. High incidence of T cell leukemia in Indian population and cytogenetic abnormalities that predict poor outcome are more common

AIM OF THE STUDY

To study the outcome of children with Acute Lymphoblastic Leukemia admitted at Government Rajaji Hospital from the year August 2003 to July 2008, a total period of five years.

OBJECTIVES:

PRIMARY:

To know the outcome of Acute Lymphoblastic Leukemia patients diagnosed and treated in GRH

SECONDARY:

1. To analyze the risk factors causing relapse and poor outcome in treated patients

2. To assign a risk classification with a available clinical and laboratory datas

DESIGN AND SETTINGS

STUDY DESIGN:

Prospective and retrospective study.

STUDY PERIOD:

Retrospective study from august 2003 to November 2006.

Prospective study from December 2006 to July 2008

STUDY PLACE:

Hospital based study conducted in the hematology ward, Institute of child health and research centre, Government Rajaji Hospital, Madurai, Tamilnadu, India.

STUDY POPULATION:

All confirmed cases of Acute Lymphoblastic Leukemia who were enrolled and on treatment during the study period were the subjects of the study.

SAMPLE SIZE: 92 patients

INCLUSION CRITERIA:

All cases of Acute Lymphoblastic Leukemia diagnosed and treated in hemato-oncology ward

EXCLUSION CRITERIA: nil

MATERIAL AND METHODS

Case Selection:

All confirmed cases of Acute Lymphoblastic Leukemia who were enrolled at the start of the study and who were diagnosed earlier and on treatment during the study period were the subjects of the study. The project was approved by hospital ethics committee and due consent was obtained from the patient's parents before the start of the study.

A thorough history was taken and followed with a detailed physical examination in each case. The case sheets of patients diagnosed with leukemia and undergoing treatment during the same period were collected from the Medical Record Department of Government Rajaji Hospital, Madurai and analyzed. Registers in Hemato oncology ward and patient's records were also analyzed. Data collected were entered in a structured proforma.

The following investigations were performed for each case. Hemoglobin, total count, differential count, platelet count, serum uric acid, base line liver and renal function test, chest x-ray, Electro cardiogram, Echo cardiogram, Ultra Sonogram abdomen, CSF analysis for malignant cells. Cytochemical studies, immunephenotyping were done for selected cases.

Possible microbiological investigation and imaging studies were performed in appropriate cases.

Treatment:

All patients diagnosed were treated with the common protocol MCP 841 without any risk categorization considering all patients at high risk.

Duration for treatment was for 22 months. All the cases who were on and completed chemotherapy were followed up regularly.

Outcome of ALL patients is analyzed as

1. **Alive without relapse**

2. Alive with relapse

3. Death before first remission

4. Death after remission and relapse

Correlation between outcome and individual prognostic factor was made.

With the available clinico pathological date a risk scoring was done and correlated with the outcome.

Prognostic factors:

Age, sex, WBC count at the time presentation, Hb, platelet count, liver size, spleen size, lymphadenopathy, presence or absence of mediastinal

lymphadenopathy, FAB morphology, no of blasts in bone marrow and the rapidity of response to therapy were analyzed with the outcome.

RISK SCORING

S. No.	Prognostic factor	Good prognosis	Poor prognosis	Very poor prognosis
1.	Age	>2, <10[0]	1-2, >10[1]	<1[2]
2.	Sex	Female[0]	Male[1]	
3.	WBC count	<10,000[0]	10,000 - 50,000[1]	>50,000[2]
4.	Platelet count	>1,00,000[0]	50,000-1,00,000[1]	< 50,000[2]
5.	HB	>8[0]	5 – 8[1]	< 5[2]
6.	FAB morphology	LI[0]	L2 or L3[1]	
7.	No of bone marrow blasts	<50[0]	50 – 90[1]	>90[2]
8.	Liver size [more than the span of their age]	Nil[0]	< 5 cms	>5cms[2]
9.	spleen size	Nil[0]	<5cms[1]	>5cms[2]
10.	Lymph node size	Nil[0]	< 3 cms[1]	> 3cms[2]
11	Mediastinal lymphadenopathy	Absent[0]	Present[1]	
12	Disappearance of blasts in PS	With in 7 days[0]	7-14 days[1]	>14 days[2]

RISK STRATIFICATION: A score of 0' was allotted for a prognostic factor with good prognosis; a score of 1' was allotted to the factor with poor prognosis and a score of 2 for with very poor prognosis :

If the score is below 8	low risk
If the score is between 8-14	high risk
If the score is 15 and more than 15	very high risk

After allotting different risk groups, the correlation between these groups and the outcome was drawn.

Sample collection and processing:

On suspicion of leukemia, bone marrow was aspirated from the iliac crest of patients. Slides were prepared and then dried for cytochemical staining with in 48 hours.

5ml of heparinized venous blood sample were taken for immunophenotyping analysis.

Periodic Acid Schiff staining:

Procedure: The air dried blood films are fixed for one minute at room temperature in formalin ethanol fixative solution and then rinsed for one minute in running tap water. The slides are then immersed in periodic Acid Schiff solution followed by rinsing in several changes of distilled water. This is followed by immersion in Schiff reagent and then washing in running

tap water for five minutes. The slides are then counter stained in hematoxylin solution. The slides were then examined under the microcopy for PAS positivity in block pattern

Data Analysis

Computer analysis of statistical data was done. Using the epidemiological information package [2002] developed by World Health organization. P value was calculated using chi-square test.

RESULTS

Total no of cases registered are 92. 33 cases are alive and 51 cases died.6 cases were absconded with case sheet. One case was referred to Chennai and lost follow up. One case was not on follow up after 2nd maintenance. Age, sex and outcome details are available for 92 patients. Complete clinical and laboratory details are available for 73 patients only. The details of 11 patients could not be traced.

AGE: 51 cases were in the age between 2-6 years [54.52%]. 12cases were >10years of age. 3 cases were in the age group of 1-2 years. Infantile leukemia is about 2.2%.

SEX: 52cases are males and 40 cases are females. Male: female ratio is 1.3

PRESENTING SYMPTOMS:

Out of 73 cases 71 [96.6%] cases presented with fever. Neck swelling was the presenting complaint in 40 cases [54.7%] and abdominal distension in 52 cases [53.4%]. 30cases were [42.8%] presented with bleeding manifestations at the time of diagnosis. Bone pain was complained in 20 cases [27.3%].2cases presented with joint pain only. Testicular enlargement was present at the time diagnosis in one case [1.3%]. One case presented with loss of vision and another case with paraplegia

PHYSICAL EXAMINATION:

Pallor was noticed in 70 cases [95.8%] .Significant lymphadenopathy was present in 62 cases [84.9%], and bleeding manifestations in 32 cases [43.8%].Bony tenderness noticed in 30 cases [42.8%].Bilateral testicular enlargement noted in one case [1.3%]. Bilateral parotid enlargement was present in 16 cases [21.9%]. Hepatomegaly was present in all cases. Liver was palpable more than 5 cm in 60% Cases. Splenomegaly was present in 70 cases [95.8%]. 3 cases were without splenomegaly. More than half of them had a spleen size of more than 5 cm .one case presented with bilateral Sub retinal hemorrhage

LABORATORY FINDINGS:

Hemoglobin : This was less than 5gms/ dl in 34 case [46.5%] and less than 8gms/dl in 84.9% cases.11 cases were with a hemoglobin between 8-11.**WBC count**: Majority of ALL [52%] had WBC counts between 10,000-50000/cumm , 24.6% with <10,000 and 23.2% with a count of >50000 at the time of presentation. **Platelet count:** nearly 65% cases presented with a platelet count of <50,000 at the time of Diagnosis .Only nine cases [12.3%] had the count of more than one lakh. The remaining 16 cases [21.9%] had the counts between 50,000-100,000.

PERIPHERAL SMEAR:

No of blasts	**No of cases**	**Percentage**
0	9	12.3%
<50	11	15%
50-90	38	52%
>90	15	20.5%

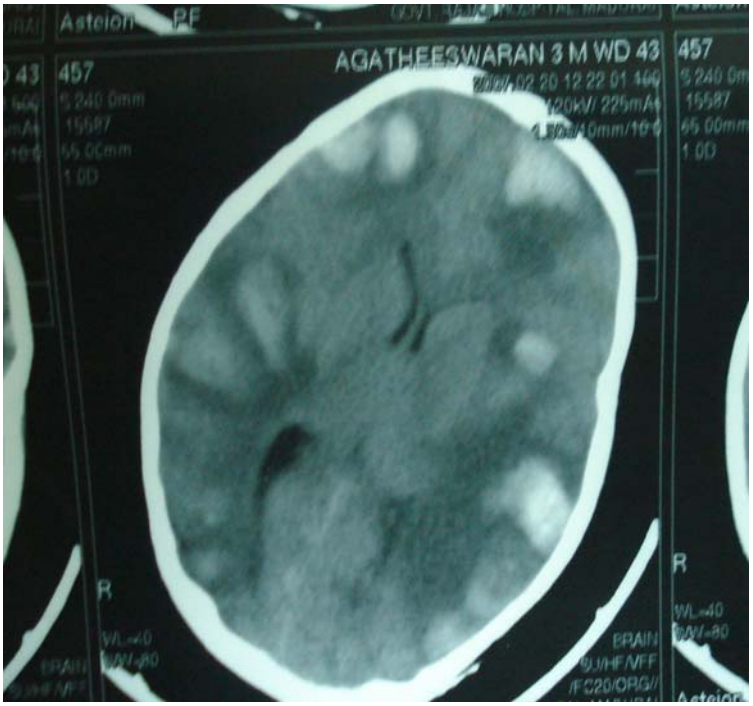
BONE MARROW EXAMINATION:

No of blasts	No of cases	Percentage
>90	21	28.7%
50-90	47	64.38%
<50	5	6.8%

FAB morphology: L1 morphology was in 40 cases [54.7%] and L2 in 33 cases.

IMMUNO PHENOTYPING: done for nine cases only. Precursor B–ALL was typed in 5 cases and mature B cell ALL in one case.3 cases [33.3%] had

ECTHYMA GANGRENOSUM WHICH YIELDED PEUDOMONAS ON CULTURE



DIFFUSE LEUKEMIC INFILTRATION IN THE BRAIN PARENCHYMA

T cell ALL 2 cases of T cell ALL relapsed and died. 1 case is on treatment. 2 cases of B cell ALL died one had relapsed. 3 cases on chemotherapy.

MEDIASTINAL LYMPHADENOPATHY:

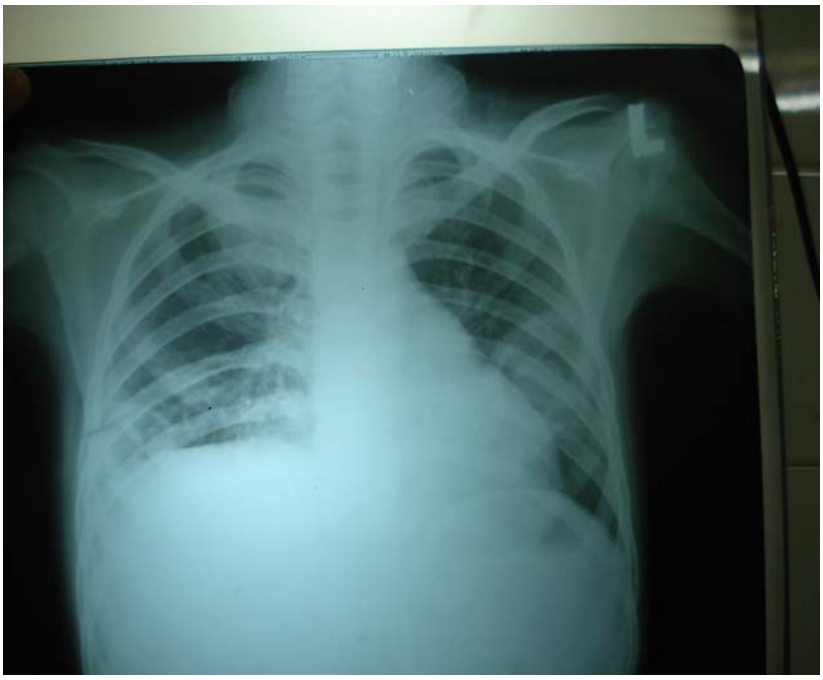
11 cases were presented with [15%] mediastinal lymphadenopathy at the time of Presentation. Immunophenotyping was not done for these cases

RENAL ENLARGEMENT:

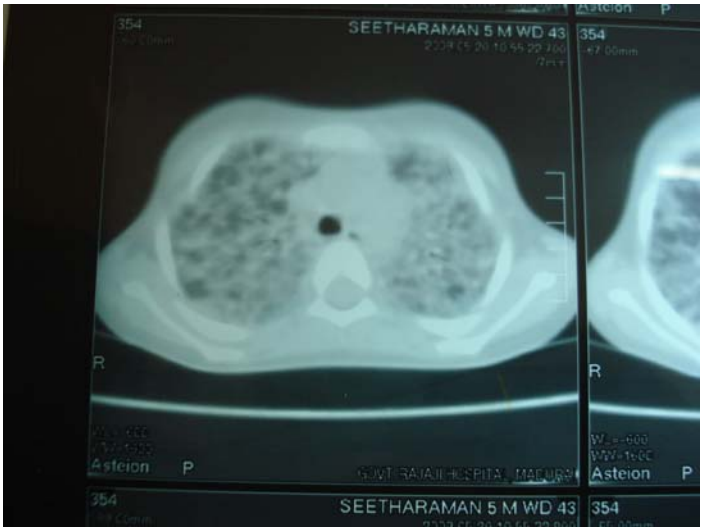
Bilateral renal enlargement was present in 5 cases and unilateral renal swelling in one case [9.5%].One case with renal failure and died before starting on chemotherapy. Only one case completed chemotherapy and is alive now. Remaining four cases were relapsed and died.

CNS INVOLVEMENT:

Two cases were presented with CNS involvement at the time of presentation [4.1%].One case with multiple parenchymal infiltrations in brain and died before starting Chemotherapy. Another case was presented with paraplegia, spinal infiltration and renal involvement along with CNS leukemia and died before remission .The third case developed sub retinal hemorrhage along with CNS involvement during chemotherapy.



SUSPECTED CASE OF PULMONARY ASPERGILLOSIS AND DIED DUE TO MASSIVE HEMOPTYSIS



PNEUMO CYSTOSIS CARINII [JIROVECI] PNEUMONIA

OPHTHALMOLOGY:

One case presented with sub retinal hemorrhage and one case developed the same during chemotherapy. One case developed exposure keratitis due to 7th nerve palsy and resolved. One case developed corneal opacity after an infectious episode in the eye.

SKELETAL:

One case was presented with leukemic infiltrate in vertebrae. Another Case developed tuberculosis of spine after therapy. Four cases had fracture during therapy.

PULMONARY:

Five cases had radio logically proved lobar consolidation. One case was suspected of pulmonary aspergillosis and died due to massive haemoptysis during induction. One case developed pneumocytosis carinii pneumonia during maintenance and recovered.

RAPIDITY OR RESPONSE:

29 cases [49.6%] showed absence of blasts in the peripheral smear after seven days of chemotherapy, 20 cases [33.8%] after 7- 14 days of chemotherapy and 14.5% of cases after 14-28 days of chemotherapy. Two cases had blasts even after one month of therapy

RESULTS ON OUTCOME

Total no of cases registered : 92

Total no of **alive c**ases : 33

Total no of **deaths** : 51

Lost follow up : 8

1. Absconded : 7

2. Referred to higher centre : 1

Total no of **relapse** cases : 28

Alive - 7 cases

Death - 21 cases

YEARWISE DISTRIBUTION OF CASES

Year [from July]	**Total no cases**	**alive**	**Death**	**Lost follow up**	**Relapse**
2003 - 2004	30	6	22	2	13
2004 - 2005	21	6	12	3	8
2005 - 2006	13	7	5	1	4
2006 - 2007	14	7	5	2	3
2007 - 2008	14	7	7	--	--
Total	92	33	51	8	28

OUTCOME OF LIVE CASES:

Total no of cases	33
Completed chemotherapy	14
On chemotherapy	19

Completed chemotherapy:

Completed chemotherapy and in remission : 14

Completed chemotherapy but relapsed : 3

and on chemotherapy

One case had relapse in the sclera after 6 months of therapy. Another case had testicular relapse followed with bone marrow relapse after 9 months of therapy. Third case had isolated testicular relapse after one year of therapy.

EVENT FREE SURVIVAL: Event free survival is calculated for patients who completed chemotherapy and in remission. Duration was calculated from the starting day of chemotherapy to July 2008

Survival in years	**No of cases**	**Percentage**
4 years	5	5.4%
3 years	10	10.8%
2 years	14	15.2%

ON CHEMOTHERAPY: Total no cases on chemotherapy: 19

S. No	On chemotherapy	Total no cases
1.	a. **Completed chemotherapy but relapsed and in chemotherapy**	3
	On 1st Maintenance	1
	On 2nd Maintenance	1
	On Induction	1
2.	**b. Relapsed during chemotherapy**	4
	On 1st maintenance	3
	On re induction	1
3.	**C .Without relapse**	12
	On 5th maintenance	3
	On 4th maintenance	1
	On 3rd maintenance	2
	2nd maintenance	2
	On 1st maintenance	3
	On consolidation	1

Total no. cases : 92

Total no live cases : 33

Overall survival rate : 35.8%

OUTCOME OF DEATH CASES:

Total no cases : 51

Outcome is analyzed in the three ways of death in these patients

S. No.	Death	No. of cases	Percentage
1.	Before starting chemotherapy	11	21.5%
2.	Before first remission	19	37.2%
3.	After remission and relapse	21	41.1%

YEARWISE DISTRIBUTION OF DEATH CASES:

Year	**Before chemotherapy**	**Before first remission**	**After remission [relapse]**
2004	3	8	12
2005	3	3	7
2006	2	3	-
2007	1	2	2
2008	2	3	-
TOTAL	11	19	21

CAUSE OF DEATH:

Death details were available for 40 patients only. In majority of the cases the cause of the death was bleeding [85%].Five cases [12.5%] died due to sepsis. One case died due to extensive leukemic infiltrate in the brain

OUTCOME OF RELAPSE:

Total	**28**	**Percentage**
Alive	7	25%
Death	21	75%

Total no of cases registered : 92

Total no of relapsed cases : 28

Relapse rate : 30.4%

Most common site of relapse was bone marrow. Next to that was testicular relapse.22 cases were males. Most of the relapses were during maintenance period only. The outcome of the relapsed patients was death in more than two-third of cases.

SITES OF RELAPSE

Total	**28**	**100%**
Bone marrow	21	75.2%
Testicular	6	21.4%
CNS	1	3.4%

CNS relapse case also had bone marrow relapse. Among six patients with testicular relapse two were with isolated testicular relapse and the remaining four with bone marrow relapse

TIME OF RELAPSE:

cycle	**alive**	**death**
Re induction	1	-
Maintenance-1	1	8
Maintenance-2	0	9
Maintenance-4	1	2
Maintenance-6	1	2
After completing chemotherapy	3	-

CORRELATION BETWEEN PROGNOSTIC FACTORS AND OUTCOME

Complete details were present for 73 cases only. Correlation was made between the outcome and twelve prognostic factors for 73 patients. Score of **0** was given to a factor with **good prognosis**, score of **1** for **poor prognosis** and a score of **2** for with **very poor prognosis.**

AGE:

Prognostic factor			Outcome				Total 73
			A	AR	D	DR	
AGE	**0**	>2, <10	21	5	18	12	56
			37.5%	8.9%	32.1%	21.4%	100.0%
	1	1-2; >10	5	1	5	4	15
			33.3%	6.6%	33.3%	26.6%	100.0%
	2	<1;			2		2
					100.0%		100.0%

P value: 0.170 >0.05 is not significant [A-alive, AR-alive after relapse, D-death, D-death after relapse]

There is no correlation between age and the outcome. Age is not a significant risk factor in predicting the outcome

SEX:

Male –score 1

Female—score 0

Prognostic factor			Outcome				Total 73
			A	AR	D	DR	
Sex	1	Male	15	6	13	8	42
			35.7%	14.3%	31.0%	19.0%	100.0%
	0	Female	11	-	12	8	31
			35.5%	-	38.7%	25.8%	100.0%

P value: 0.245 >0.05% not significant

There is no correlation between sex and the outcome. Sex is not a significant risk factor in predicting the outcome.

WBC COUNT:

WBC count <10,000/cumm - 0 score

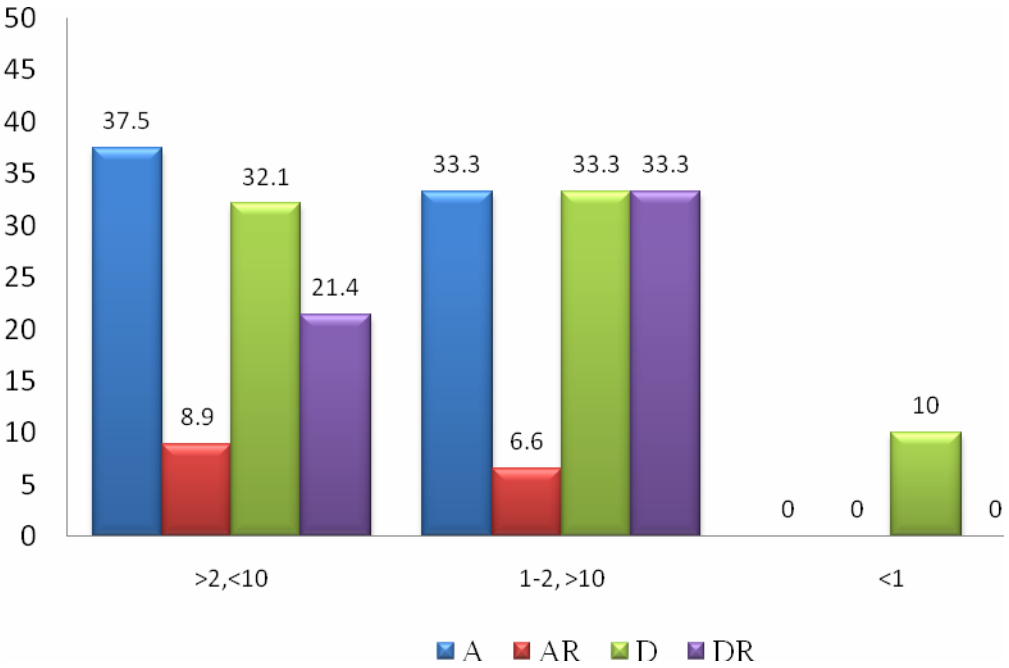
10,000-50,000/cumm - 1 score

>50,000/cumm - 2 score

Prognostic factor			OUTCOME				Total 73
			A	AR	D	DR	
WBC COUNT	0	<10,000	11	4	2	1	18
			61.2	22.2%	11.1	5.6%	100.0%
	1	10,000-50,000	11	0	16	11	38
			46.8%	9.3%	31.2%	12.5%	100.0%
	2	>50,000	4	2	7	4	17
			23.5%	11.8%	41.2%	23.5	100.0%

P value 0.001. < 05 is significant.

There is a definite correlation between WBC count and the outcome as a prognostic factor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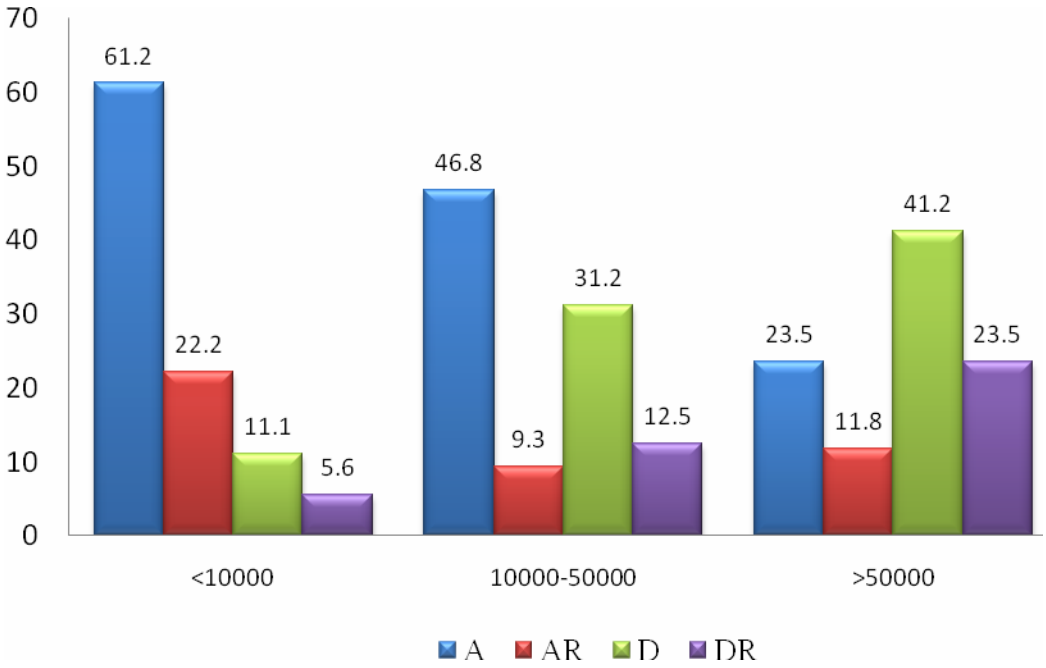
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PLATELET COUNT:

Platelet count:

> 1,00,000 - 0 score

50,000-1,00,000 - 1 score

<50,000 - 2 score

Prognostic factor			OUTCOME				Total 73
			A	AR	D	DR	
PLATELET	0	> 1 LAKH	7		2		9
			77.8%	3	22.2%		100.0%
	1	50,000-1 LAKH	10	2	2	2	16
			62.5%	12.5%	12.5%	12.5%	100.0%
	2	<50,000	9	4	21	14	48
			18.8%	8.3%	43.8%	29,2%	100.0%

P value 0.0001 <0.05 is significant.

There is definite correlation between platelet count and the outcome as a prognostic factor.

HEMOGLOBIN:

Hemoglobin: >8gms/dl - 0 score

5-8gms/dl - 1 score

<5gms/dl - 2 score

Prognostic factor			outcome				Total 73
			A	AR	D	DR	
HEMOGLOBIN	0	>8	6	2	2	1	11
			54.5%	18.2%	18.2	9.1%	100.0%
	1	5-8	11	3	9	5	28
			39.3%	10.7%	32.2%	17.9%	100.0%
	2	<5	9	1	14	10	34
			35.6%	8.2%	34.2%	31.9%	100.0%

P value 0.225. > 0.05 not significant

There is no correlation between hemoglobin and the outcome. Hemoglobin is not a significant risk factor predicting the outcome

MEDIASTINAL LYMPHADENOPATHY:

Absent - 0 score

Present - 1 score

Prognostic factor			Outcome				Total 73
			A	AR	D	DR	
Mediastinal lymph adenopathy	0	absent	30	5	11	16	62
			48.1%	31%	17.7%	26%	100%
	1	present	2	3	1	5	11
			18.1%	27.2%	9.09%	45.4%	100%

P value 0.024 <0.05 is significant.

There is a definite correlation between mediastinal lymphadenopathy and the outcome as a prognostic factor

LYMPH NODE SIZE:

No significant lymphadenopathy - 0 score

Size less than 3 cm - 1 score

Size more than 3 cm - 2 score

Prognostic factor			Outcome				Total 73
			A	AR	D	DR	
LYMPH NODE SIZE	0	NIL	9	- -	-	2	11
			81.8%	-	--	18.2%	100.0%
	1	<3 CM	10	4	12	6	32
			34.5%	13.8%	41.4%	10.3%	100.0%
	2	>3 CM	5	2	12	11	30
			17.9%	7.1%	42.9%	32.1%	100.0%

P value 0.001. <0.05 is significant.

There is a definite correlation between lymph node size and the outcome as a prognostic factor

LIVER SIZE:

Score 0 - normal liver span for corresponding age

Score 1 - increased liver span for the age, <5 cm

Score 2 - increased liver span for the age, > 5cm

Prognostic factor			outcome				Total 73
			A	AR	D	DR	
LIVER SIZE	0	NIL	-	-	-	-	-
			-	-	-	-	-
	1	<5CM	16	4	7	2	29
			55.2%	13.8%	24.1%	6.9%	100.0%
	2	>5CM	10	2	18	14	44
			22,7%	4.5%	40.1%	31.8%	100.0%

P value 0.004. <0.05 is significant.

There is definite correlation between liver size and the outcome as a prognostic factor

SPLEEN SIZE:

No splenomegaly - 0 score

Spleen palpable <5cm - 1 score

Spleen palpable >5cm - 2 score

Prognostic factor			outcome				Total 73
			A	AR	D	DR	
SPLEEN SIZE	0	NIL	1	1	-	1	3
			33.3%	33.3%	-	33.3%	100.0%
	1	<5CM	15	3	10	4	32
			46.8%	9.3%	31.2%	12.5%	100.0%
	2	>5CM	8	1	17	12	38
			21.0%	2.6%	44.7%	31.5	100.0%

P value 0.031 <0.05 is significant.

There is a definite correlation between spleen size and the outcome as a prognostic factor

FAB CLASSIFICATION

L1 morphology - 0 score

L2 morphology - 1 score

Prognostic factor			Outcome				Total 73
			A	AR	D	DR	
FAB	0	L1	16	4	14	6	40
			40.0%	10.0%	35.0%	15.0%	100.0%
	1	L2	10	2	11	10	33
			30.3%	6.06%	33.3%	30.3%	100.0%

P value is 0.245 >0.05 is not significant.

There is no correlation between the FAB morphological classification and the outcome as a prognostic factor

BONE MARROW BLASTS

No of blasts if <50 - 0 score

No of blasts if 50-89 - 1 score

No of blasts > 90 - 2 score

Prognostic factor			Outcome				Total 73
			A	AR	D	DR	
BONE MARROW BLAST	0	N<50	5				5
			100				100.0%
	1	50-89	17	5	14	11	47
			36.2%	10.6%	29,8%	23.4%	100.0%
	2	>90	4	1	11	5	21
			19%	4.8%	52.4%	23.8	100.0%

P value is 0.020 <0.05 is significant.

There is a definite correlation between the no of the bone marrow blasts and the outcome as a prognostic factor

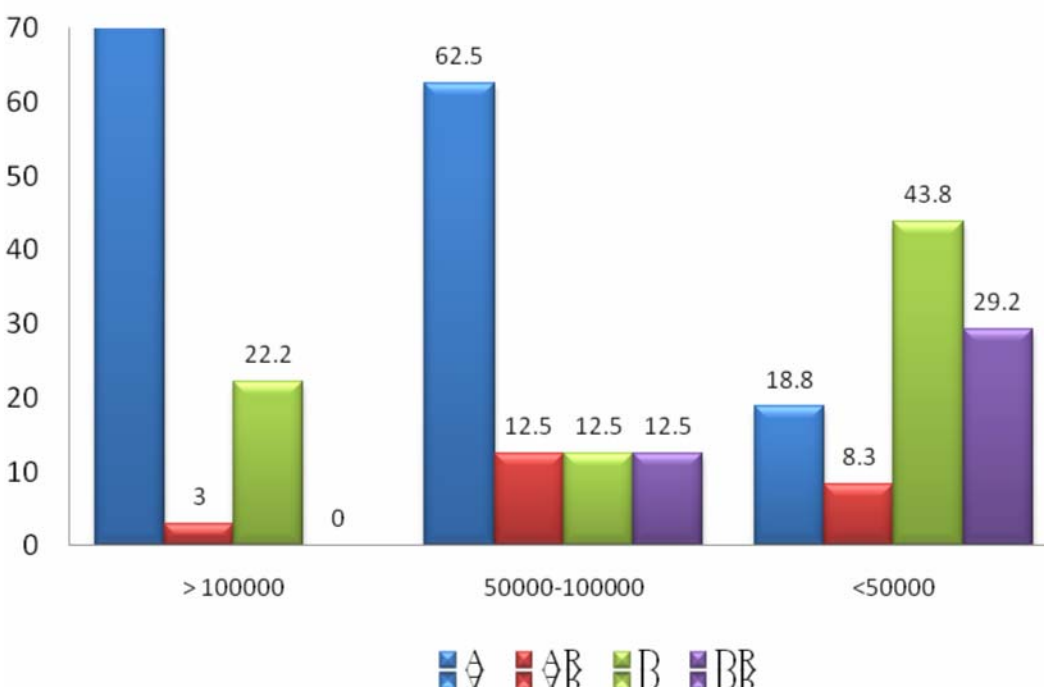
RAPIDITY OF RESPONSE:

11 cases died before starting chemotherapy. So the rapidity of response was noted in 59 cases only.

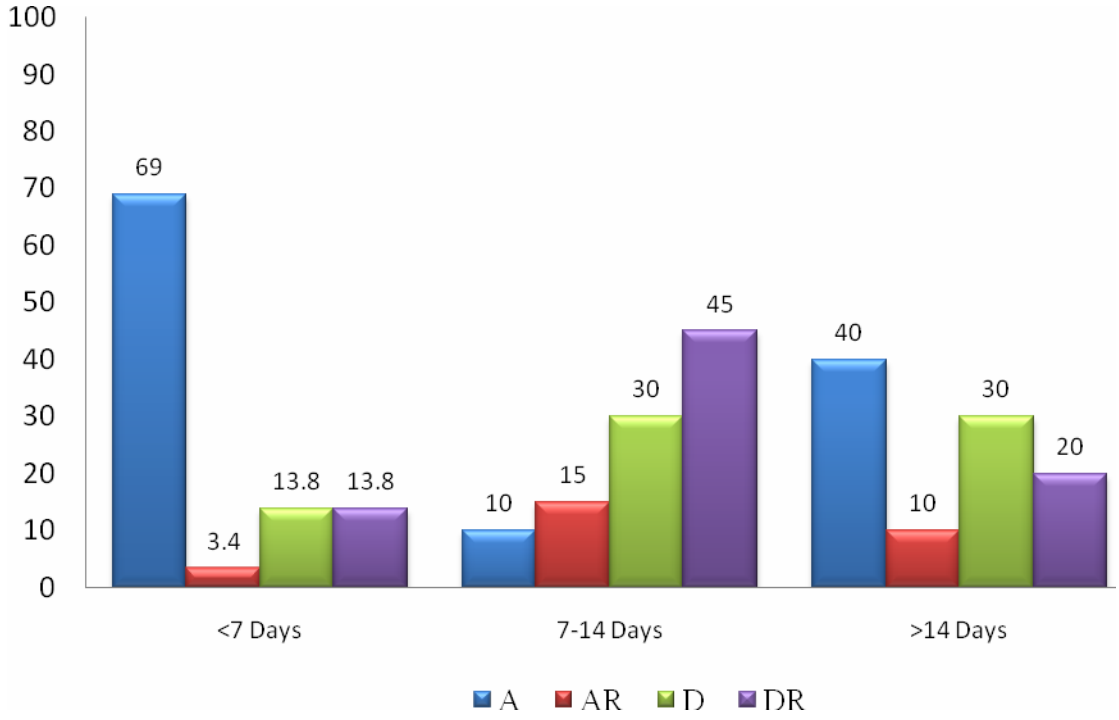
Prognostic factor			Outcome				Total 59
			A	AR	D	DR	
DISAPPERANCE OF BLASTS IN PS	0	<7 DAYS	20	1	4	4	29
			69%	3.4%	13.8	13.8%	100.0%
	1	7-14 DAYS	2	3	6	9	20
			10%	15%	30%	45%	100.0%
	2	>14 DAYS	4	1	3	2	10
			40%	10%	30%	20	100.0%

P value 0.007 < 0.05 is significant. There is a definite correlation between rapidity of response and the outcome as a prognostic factor

There is a **significant and definite correlation noted** between initial white blood cell count, platelet count, mediastinal lymphadenopathy, lymph node size, liver size, spleen size, no of bone marrow blasts and rapidity of response with the future outcome and relapse. There is **no correlation between** age at the time of presentation, sex, hemoglobin and FAB morphology and outcome



RAPIDITY OF RESPONSE

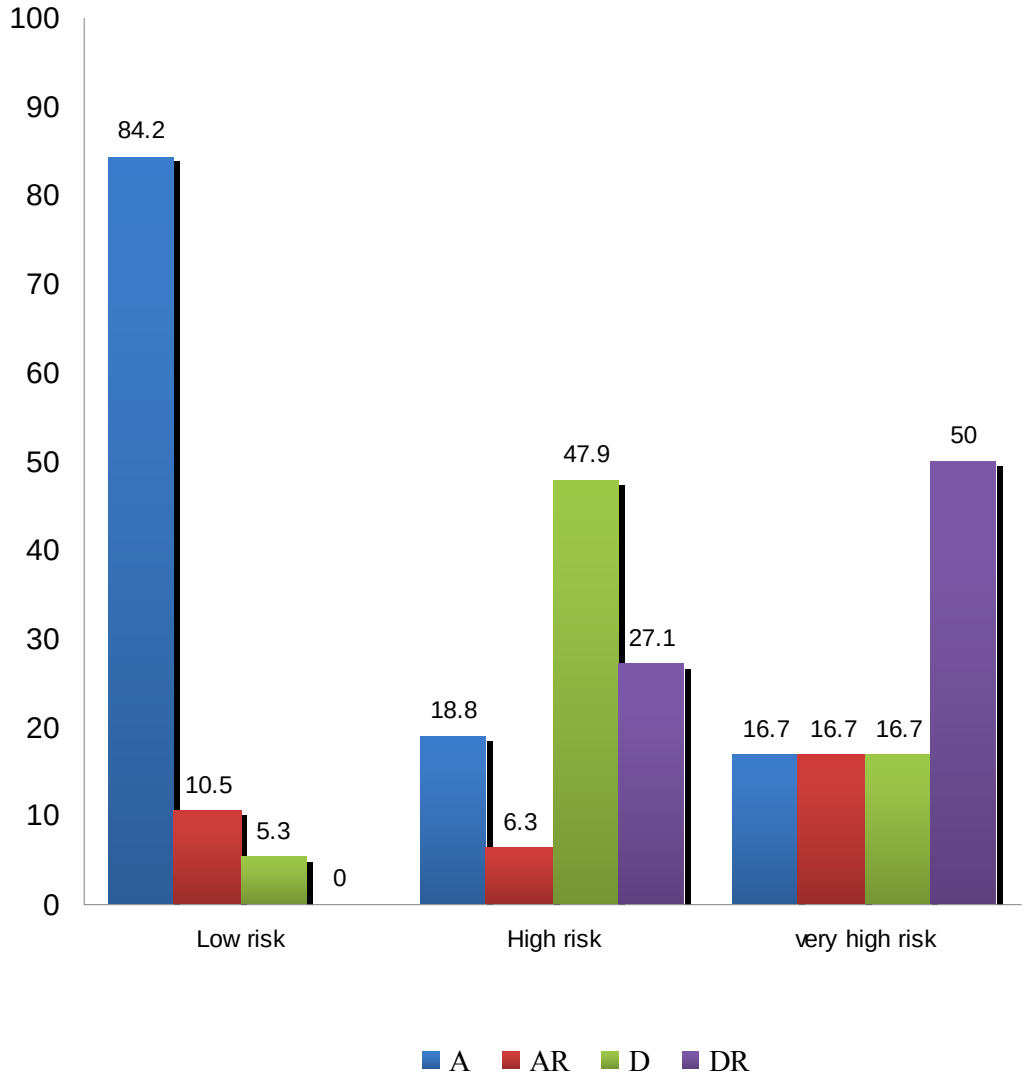


RISK SCORING: After summing the all scores for prognostic factors

RISK SCORING			OUTCOME				Total 73
			A	AR	D	DR	
RISK SCORING	LOW RISK	<8	16	2	1	0	19
			84,2%	10.5%	5.3%	-	100.0%
	HIGH RISK	8-14	9	3	23	13	48
			18.8%	6.3%	47.9%	27.1%	100.0%
	VERY HIGH RISK	>15	1	1	1	3	6
			16.7	16.7%	16.7%	50%	100.0%

P value 0.0001. <0.05 is significant. There are 19 patients in low risk category. 18 patients are alive with only one death. There are 48 patients in high risk category.36 cases were died and only 12 cases are alive with relapse of three cases. There are 6 patients in very high risk category. 4 cases were died and only 2 cases are alive and with relapse of one case. **There is a poorer outcome with patients of high and very high risk patients than with patients of lower risk.**

SCORING



Low risk cases showed good prognosis than high risk and very high risk cases.

DISCUSSION

AGE:

In accordance with literature the most common age group was 2-6 Years [1,2,3]. Infantile leukemia was constituting about 2.2% of the total cases as compared to 3-5% in other reviews [9,10]

SEX:

There was a definite male preponderance in the study with male to female ratio of 1.35:1. It is comparable with western [1,9] as well as Indian literatures [18].

PRESENTING COMPLAINTS

Fever was present in 95% of cases in this study. It is a very common Presentation in Indian studies than in western. Bleeding was present in 43.8% of cases and is comparable with the other studies

symptoms	Present study	Bangalore study [18]	Other reviews[9,10]
fever	95%	56.7%	61%
bleeding	43.8%	30%	48%
Bone pain	42.8%	46.7%	28%
Pallor	95.8%	100%	100%
Testicular involvement	1.3%	nil	25%
CNS involvement	4.1%	3.3%	5%

Physical examination:

Hepatomegaly and splenomegaly were noted in >90% of cases which is comparable with most of the Indian studies in contrast with many western studies [9,10]. Lymphadenopathy was present in >80% of cases. But from western statistics it is only about 50%

Clinical feature	**Manipur study[18]**	**Tata memorial[45]**	**AIIMS study[37]**	**Other reviews[9,10]**	**Present study**
hepatomegaly	100%	80%	95%	68%	100%
splenomegaly	98%	78%	90%	68%	95.8%
lymphadenopathy	76.7%	79%	87%	50%	84.9%

Lab parameters: HB, WBC count and platelet count is comparable with other studies

Lab parameter	Manipur study[18]	Other reviews[1,9,10]	Present study
HB <10 gms	96%	80-85%	90%
WBC count >% >50,000	20%	17%-25%	23.2%
Platelet count <50,000	73%	45%	65%

Morphological classification:

L1 and L2 are [54.7%, 45.3%] equally distributed in leukemic cases

In contrast with the other reviews [4,5,16,18] where L1 morphology is more common

Immunophenotyping:

B cell in 65%, T cell in 35% and was noted in this study. From other studies [9,10] T cell leukemia it is 15-22% supporting the evidence of higher incidence of T cell ALL in Indian population. T cell was associated with poor prognosis.

Mediastinal lymphadenopathy is noted in 15% of the cases against 7% in other western studies [64] Renal involvement was noted in 9.5% of cases .18% in other reviews and associated with poor prognosis [50,64] .Parotid gland enlargement is noted in 21.9% of cases with poor prognosis [49]

Rapidity of response:

Among 59 patients 29 cases [49.1%] showed disappearance of blasts in the peripheral smear with in seven days and 20 cases [33.8%] within 7-14 days. 8 cases had persistence of blasts in 14-28 days of chemotherapy. 2 cases had blasts in peripheral smear even after 1 month of induction therapy. More than 50% of cases showed poor response and poor prognosis.

OUTCOME OF PATIENTS:

Event free survival rate is lower in the present study than that of from other studies

EFS	Chennai study 2002 [59]	Tata memorial hospital 1999[45]	China study2005 [12]	National cancer institute 2008[25]	Present study 2008
2 years	41%				15.2%
3 years	31%				10.8%
4 years	18%		52.3%		5.4%
5years		53%		85-88%	
T cell infancy Very high risk		45%		62% 10-30% <45%	

Overall survival rate is **35.8%** which is about 59.8%, 57.6% in the vellore [27] and a china [12] study respectively.

Outcome of death cases:

21.5% of cases died before starting chemotherapy with high induction deaths. Cause of death was mainly bleeding in this study in contrast with many [22,24] other reviews where infection was the common cause of death

Outcome of relapses:

Relapse rates were comparable with Mumbai study and was more than that of AIIMS study and many western studies [42, 44].

	AIIMS study[37]	China study[12]	Mumbai study[45]	Present study
Relapse rate	17.1%	24.1%	29.9%	30.4%

Most common site of relapse is bone marrow followed with testicular relapse which is 8.2% comparable with other reviews [9, 10]. Relapses were more common in male cases than females and most of them during maintenance period [41]. Only 30% are alive after relapse [9,10]

RISK FACTORS ANALYSIS

From study in Japan [58] age, sex and response to treatment were very significant factors. In FARLLE [57] study high WBC [p value 0.001], mediastinal mass [0.017] and the response [0.001] were significant

RISK FACTORS ANALYSIS

FACTORS	PRESENT STUDY P VALUE	CCG1978-1983 AND [13]HAMMOND ET AL STUDY1986	CHENNAI STUDY2002[59]
Age	0.170[ns]	<0.0001	
Sex	0.245[ns]	<0.0001	
WBC count	0.001[s]	<0.0001	0.001
platelet	0.0001[s]	<0.0003	0.006
Hemoglobin	0.225[ns]	0.53	
Liver	0.004[s]	<0.0006	-
Spleen	0.031[s]	0.19	-
lymph node	0.001[s]	0.59	-
med adenopathy	0.024[s]	<0.0001	0.017
BM blast	0.020[s]	-	-
FAB	0.429[ns]	<0.0004	-
Rapidity of response	0.007[s]	<0.0001	-

LIMITATIONS OF THE STUDY

1. Risk stratification was not done for cases in this study.
2. Immuno phenotyping was done for only 9 cases.
3. Cyto genetic analysis and minimal residual disease were not done for cases to predict the outcome.
4. No separate regimen for T cell which is highly prevalent in India than in western countries and with poor prognosis.
5. 8 cases were lost follow up in this study.

CONCLUSIONS

1. There was a definite male preponderance with a peak age group was between 2-6 years
2. Hepatomegaly was noted in 100% of cases. Splenomegaly in 95%and lymphadenopathy in 85% of the cases .CNS ivolvement in 4.1% of cases
3. Severe extra medullary disease, renal involvement and parotid gland involvement were associated with poor prognosis
4. WBC count at the time of presentation, platelet count, hepatosplenomegaly, lymphadenopathy, mediastinal lymphadenopathy, bone marrow blasts and the rapidity of the response were found to be statistically significant prognostic factors predicting the outcome and relapse
5. There was no correlation between age, sex, hemoglobin and FAB morphology with the outcome
6. This clinico-pathological risk scoring is simple. can be done in all peripheral hospitals as it does not require any advanced and costly techniques like immunophenotying and cytogenetics.It was found to be statistically significant

7. Event free survival at 2,3 and 4 years are 15.2%,10.8%and 5.4% respectively and it is lower than that of other Indian and western reviews
8. Relapses were noted in 30.4%of cases.
9. Most common site was bone marrow. Testicular relapse was noted in 8.2% 0f the cases
10. Most of the relapses were noted in males and during maintenance phase
11. 20% of deaths were before starting chemotherapy and 40% of the deaths before remission
12. Bleeding was the cause of the death in nearly 80% of the cases
13. Poor prognosis noted in this study could be due to high incidence of extramedullary disease, T cell leukemia, higher rates of death during induction, poor supportive care and lack bone marrow transplantation facilities in our set up

RECOMMENDATIONS

1. Risk stratification will be useful to predict the long term outcome of the patients and segregate the high risk patients. This risk scoring with the available and possible datas can be very useful, low cast and applicable to all peripheral hospitals which are the treating places of leukemia in this less privileged country
2. Immuno phenotyping and cytogenetic analysis should be done for all case to find out high risk cases. Those high risk cases can be referred to higher and specialized oncology centres
3. Prednisolone response before chemotherapy and 14^{th} day marrow after chemotherapy can predict the long term outcome when other prognostic factors losing the significance.
4. Most of the relapses were during maintenance. So adding monthly **vincristine** and steroids may be helpful to prolong the remission in patients.
5. Separate regimen for T cell patients may be useful to overcome the low event free **survival** rate in our Leukemia patients.
6. As nearly 70-80% of the relapses were occurred in males and all are early and intermediate relapses we can extend the duration of therapy

from 2 years to 3 years for males as seen in other protocols of Leukemia.

7. Bone marrow transplantation which is probably the only chance of cure for these patients must be made available once they enter remission at least for relapsed cases.
8. Continuous supply of the drugs, good supportive care, adequate infection control practices and psychological supports should be made for all these patients to improve the outcome.

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PROFORMA

OUTCOME OF CHILDREN WITHACUTE LYMPHOBLASTIC LEUKEMIA IN GRH

PROFORMA

NAME : **ADDRESS:**

AGE :

SEX : **OCCUPATION:**

DATE OF DIAGNOSIS: **INCOME**

PHONE NO

PRESENT HISTORY :- **DURATION:**

H/O Fever / chills & rigor / night sweats.

H/O Abdominal Distension / Abdominal Pain

H/O Progressive pallor / easy fatigueability

H/O Petechiae / Purpura / Eccymosis

H/O Epistaxis / Haemetamesis / Haematuria / Gumbleed.

H/O Bony swelling / Bony pain / Joint pain / restriction of joint movement

H/O Neck swelling / generalized Body swelling.

H/O Breathlessness / cough / Stridor / wheeze.

H/O loss of weight / Loss of Appetite / Failure to thrive.

H/O head ache / Nausea / Vomiting / size of Head / Blurring of vision.

H/O fits / Altered Sensorium / Coma.

H/O Difficulty in speech / Gait abnormality

H/O suggesting cranial (N) palsies / Paucity of movements

H/O testicular swelling

H/O Chest pain / Palpitation / Pedal edema

H/O Orbital swelling / diplopia / loss of vision

H/O repeated blood transfusion

Others

PAST HISTORY:

Previous H/O similar episode

Previous H/O Hospitalization

Previous H/O TB / Jaundice / other illness

H/O RRI

H/O Native Medicine

ANTENATAL HISTORY :-

H/O drug intake Yes / No

H/O irradiation YES / NO

BIRTH HISTORY :-

NEONATAL HISTORY :-

DEVELOPMENTAL HISTORY :-

IMMUNISATION HISTORY :-

FAMILY HISTORY :-

H/O any Leukemia / other cancers in the family

RISK FACTORS :-

Environmental Factors

1. Ionizing radiation
2. Toxic Chemicals / Pesticide exposure

Immuno Defficency states :-

1. Down's syndrome
2. Bloom's syndrome
3. fredrick's ataxia
4. Others

GENERAL EXAMINATION

Mental status
General Condition
Febrile / Afebrile
Respiratory status
Hydration
Pallor
Icterus / cyanosis / clubbing
Dental carries / oral ulcer
Lymphadenopathy – 1 cervical
2. axillary
3. inguinal
bonytenderness / bony swelling / joint pain **RR**

Petechiae / Purpura / Eccymosis

ANTHROPOMETRY	**VITALS**
HC	**HR**
CC	**RR**
HT	**BP**
WT	
AC	**TEMP**

SYSEMIC EXMINATION

I. ABDOMEN :

INSPECTION
- Shape of the abdomen
- Movement with respiration
- Mass dilated veins, pulsations

PALPATION ;-
- Tenderness
- Liver :-
  - Size
  - Span
  - Firm / soft
- Spleen :-
  - Size
  - Consistency

Surface

Renomegaly :- Freefluid :-

PERCUSSION :-

AUSCULATION :-

GENITALS :-

II. CARDIO VASCULAR SYSTEM;

apical impulse
heart sounds
murmur

III. RESPIRATORY SYSTEM :-

Trachea Position

Size / shape of the chest

Type of respiration

Chest expansion

Percussion note

Auscultation

IV. CENTRAL NERVOUS SYSTEM :-

Higher function

Cranial (N) Examination

Motor System

Sensory System

Cerebellar System

Spine & Cranium

Gait

Fundus

INVESTIGATIONS :-

URINE : Alb
Sug
Deposits

BLOOD ; HB %
TC
DC

PLATELER COUNT
Bleeding time
Clotting Time
Blood grouping and typing

COMPLETE HAEMOGRAM

PERIPHEAL SMEAR Pathology No:

BONE MARROW STUDY Pathology No
:

IMMUNO PHENO TYPING

CYTO GENETIC STUDY

BLOOD
Urea
Sugar
Serum, Creatine
Serum Uric Acid
Serum Amylase

LFT
Bilirubin

CSF;
cells

Proteins
SGOT SGPT Alkaline Phosphatase
LDH
HBSAG,
HIV
Calcium, phosphorus

X – RAY CHEST

ULTRA SOUND ABDOMEN

ECG

ECHO

BLOOD CULTURE

URINE CULTURE

CT SCAN BRAIN / CHEST / ABDOMEN

DIAGNOSIS

ABBREVIATIONS USED

ALL	-	Acute lymphatic leukemia
AML	-	Acute myeloid leukemia
ATRA-C	-	Cytosine arabinoside
CNS	-	Central nervous system
CSF	-	Cerebro Spinal fluid.
EFS	-	Event Free survival
FAB	-	French American British
HB	-	Hemoglobin
Ig	-	Immunoglobulin
I.T	-	Intrathecal
MTX	-	Methotrexate
MRD	-	Minimal Residual Disease.
NCI	-	National Cancer Institute
PAS	-	Periodic Acid Schiff staining
POG	-	Paediatric Oncology group
WHO	-	World Health Organization
WBC	-	White Blood

S.No	Name	Date	Outcome	Age	Sex	WBC	Platelet	Hb	Liver	Spleen	Lymph Node	Media Lym	FAB	BM Blast	Response	Risk Score
1	pavithra	9.6.05	1	9	1	4400	52000	4.5	2	0	0	0	0	72	1	7
2	balasubran	3.2.05	1	7	0	10200	60000	3.4	4	7	0	0	0	70	0	10
3	nimekalai	31.7.05	1	6	1	8400	150000	10	2	2	0	0	0	72	0	3
4	balamurug	12.10.05	1	10	0	4600	150000	9	5	10	1	0	0	42	0	5
5	riyaz	16.5.05	2	6	0	6000	70000	9.8	2	1	1	0	0	65	1	7
6	balaji	6.5.05	4	5	0	12400	20000	3.8	3	3	0	0	0	90	1	11
7	sabana	3.3.05	1	7	1	110000	60000	6	6	5	0	0	0	70	0	7
9	sandhya	11.2.05	4	5	1	18000	20000	4.5	4	8	2	0	1	90	0	13
10	b.thanush	9.4.05	3	8 months	0	60000	20000	3.8	8	10	1	0	0	95		15
11	sandhya	13.4.05	4	9	1	68000	20000	3.2	10	12	1	0	0	95	1	14
12	isravel	10.4.05	3	4.5	0	11600	90000	4	5	7	2	0	1	95		15
13	sangeetha	7.5.05	3	7	1	21000	20000	5	4	2	1	0	1	71	1	10
14	roselline	12.7.05	4	10	1	70000	60000	6	8	0	1	0	1	90	1	11
15	monika	3.12.05	4	9	1	28000	20000	3.8	6	7	2	0	1	95	1	16
16	suganya	4.8.05	3	11	1	18500	20000	4	8	9	2	0	1	95		15
17	munitaraj	30.12.05	4	10	0	34000	30000	4.5	6	8	2	0	0	90	0	14
18	abdul	11.1.05	1	9	1	19500	60000	9.2	2	1	2	0	0	45	0	8
19	hari	14.1.06	1	3	0	8200	180000	6.8	3	2	0	0	0	35	0	4
20	m.selvaraj	8.2.06	2	5.5	0	6400	20000	6.2	4	0	2	0	0	80	1	9
21	sneka	20.5.06	1	4	1	9000	90000	4.6	2		0	0	0	90	0	6
22	rajesh	23.6.06	1	7	0	28000	150000	8	4	4	2	0	1	95	0	8
23	stalin	28.9.06	1	10	0	6600	30000	8	6	3	1	0	0	85	0	7
24	sabari	18.10.06	2	7	0	700	45000	8.9	2		1	0	0	55	1	6
25	vigneswara	30.6.06	2	1.5	0	6400	20000	2.8	4	2	1	0	1	60	0	10
26	baskar	11.9.06	3	4	0	21000	20000	2.8	4	3	1	0	0	95	0	11
27	manoj	9.1.06	3	2.5	0	6000	45000	5	11	8	1	0	0	80	2	11
28	arun	10.12.06	3	4.5	0	20000	20000	4.3	8	10	2	0	0	90	0	15
29	y.bhrathi	3.6.06	3	3	1	18000	20000	3.8	6	7	2	0	1	60	1	14
30	mahalaksh	17.1.06	3	2	1	60000	20000	4.6	8	4	2	0	0	95	2	15
31	mariajency	17.3.06	3	5	1	18000	60000	6.2	8	4	2	0	0	90	1	11
32	rektchi	24.1.07	4	4	1	14000	45000	6.8	8	4	2	0	0	90	1	11
33	seetharam	21.2.07	1	4.5	0	20000	60000	8.7	1		2	0	0	70	0	4
34	vinohini	9.3.07	4	4	1	16000	45000	5.6	5	8	1	0	0	90	2	12
35	priya	21.3.07	1	11	1	35500	100000	3.6	6	3	1	0	0	70	0	11
36	davin	9.3.07	1	2	0	4600	20000	6.2	3	4	0	0	0	35	0	6
37	mohan	17.7.07	1	3	0	11000	20000	4	2	2		0	1	70	2	12

S.No	Name	Date	Outcome	Age	Sex	WBC	Platelet	Hb	Liver	Spleen	Lymph Node	Media Lym	FAB	BM Blast	Response	Risk Score
38	prasanth	20.12.07	1	8	0	200000	20000	10	8	10	2	1	1	95	2	17
39	pandeswar	22.4.07	2	4	0	66400	20000	5.8	6	10	2	1	1	95	2	19
40	k.sundram	20.12.07	1	7	0	88000	52000	3.4	6	10	1	0	1	95	0	12
41	priya	25.6.07	3	3.5	1	92000	17000	4.6	6	6	1	0	1	75	0	13
42	staleeswar	24.8.07	3	5	0	28000	45000	6	8	6	2	1	0	90	2	15
43	aagathesw	16.2.07	3	3	0	95000	20000	3.8	3	4	2	0	0	95		13
44	kowsalya	11.10.07	3	1.5	0	14650	20000	5.2	4	5	1	0	1	90	1	14
45	chakkarava	19.10.07	4	4	0	22000	12000	2.8	8	9	2	0	1	95		13
46	t.selvam	11.2.08	1	8	0	7200	120000	3.6	4	2	1	0	0	75	0	7
47	vignesh	19.2.08	1	8	0	2900	72000	5.9	2	2	2	0	1	85	2	11
48	kowsalya	19.5.08	1	8	1	24000	20000	6.8	6	7	1	0	1	85	1	12
49	kumaran	2.5.08	3	3	0	20000	20000	6.6	2	2	1	0	0	85	1	10
50	simran	14.4.08	1	8	1	3500	20000	5.5	5	3	1	0	1	82	0	9
51	swedha	9.6.08	1	5	1	200000	20000	3.5	6	6	1	0	1	85	2	15
52	saran	24.1.08	3	1.5	1	18000	20000	4.2	6	3	1	0	0	96		12
53	sairabanu	25.6.08	1	8	0	45000	20000	3.6	6	6	2	0	1	90	0	15
54	suresh	25.3.08	3	11	1	139000	13000	7.8	3	3		0	1	90	0	11
55	punitha	11.3.08	3	2.5	1	24500	20000	4	8	9	1	0	1	95		13
56	stephina	16.7.08	3	6	1	8400	25000	9	4	4	1	0	0	75		6
57	prithvi	30.11.04	2	4.5	0	145000	90000	6.8	6	4	1	0	0	85		9
58	kanimozhi	30.10.04	1	4	1	6000	20000	7.8	3	2	0	0	0	95	0	7
59	thilagaraj	23.2.04	1	12	0	35000	60000	9.2	2	1	1	1	0	45	0	8
60	marisree	2.2.04	1	10	0	25000	150000	5.6	4	3	1	0	1	85	0	8
61	vignesh	6.8.04	1	3.5	1	18000	120000	6.8	3	4	0	0	0	80	0	5
62	pavithra	15.7.04	4	7	0	100000	45000	3.4	10	16	2	1	0	95	1	18
63	a.babu	18.2.04	4	10	1	6600	20000	4.8	9	10	1	0	1	90	0	15
64	harikaran	25.6.04	3	6 months	0	25000	20000	6.2	8	10	2	0	1	95	1	14
65	muthu priy	24.2.04	4	8	0	28000	18000	11.3	9	14	2	1	1	80	1	12
66	siva	24.6.04	3	1.5	0	18200	40000	7.6	8	8	2	1	0	90		16
67	padiyan	24.5.04	3	10	0	28000	45000	8.8	8	11	1	0	0	85		11
68	balasubran	13.6.04	4	3	0	58000	20000	4.2	8	6		0	1	95	1	15
69	kalimuthu	8.10.04	4	12	0	44000	20000	6.4	6	10	2	1	1	75	2	16
70	masanam	8.11.04	4	8	1	38000	40000	3.8	7	8	2	0	1	90	1	15
71	aswin	6.8.08	3	2.5	1	58000	20000	3.2	8	12	1	0	1	95		14
72	sandhiya	7.9.08	3	8	1	68000	250000	2	9	9	2	1	0	95		15
73	apsana	8.7.04	3	2.5	0	35000	150000	3.6	8	9	2	1	1	90		15